01-13-05

1617

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TRANSMITTAL FORM

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Total Number of Pages in This Submission: 37

Application Number	10/057,323
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis et al.
Art Unit	1617
Examiner Name	San-Ming R. Hui
Attorney Docket Number	CV01489K/4686-045531

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [x] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Webb Ziesenheim Logsdon Orkin & Hanson, P.C.		
Signature			
Printed name	Ann Marie Cannoni		
Date	January 12, 2005	Reg. No.	35,972

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Signature			
Typed or printed name	Chris Reichert	Date	January 12, 2005

PTO/SB/17 (12-04v2)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500.00

Complete if Known	
Application Number	10/057,323
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis et al.
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Attorney Docket No.	CV01489K/4686-045531

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 23-0650 Deposit Account Name: Webb Ziesenheim Logsdon

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x _____	= _____

4. OTHER FEE(S)

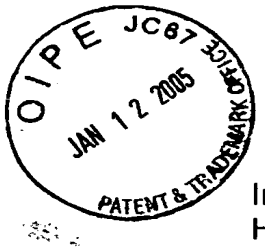
	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Appeal Brief	500.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 35,972	Telephone 412-471-8815
Name (Print/Type)	Ann Marie Cannoni		Date January 12, 2005

Response Under 37 C.F.R. §1.192
Appellant's Brief

Application No. 10/057,323
Paper Dated: January 12, 2005
Attorney Docket No. CV01489K



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of: Harry R. DAVIS, et al.	Examiner: San-Ming R. Hui
Serial No.: 10/057,323	Group Art Unit: 1617
Filed: January 25, 2002	Atty. Docket No.: CV01489K
For: COMBINATIONS OF PEROXISOME PROLIFERATOR-ACTIVATATED RECEPTOR (PPAR) ACTIVATOR(S) AND STEROL ABSORPTION INHIBITOR(S) AND TREATMENTS FOR VASCULAR INDICATIONS	

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ON APPEAL FROM THE PRIMARY EXAMINER TO THE
BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANT'S BRIEF UNDER 37 C.F.R. § 1.192

01/27/2005 CNGUYEN 00000006 230650 10057323
01 FC:1402 500.00 DA

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1/12/2005
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Chris Reichert
Typed Name of Person Signing Certificate

TABLE OF CONTENTS

Page

TABLE OF CONTENTS I

REAL PARTY IN INTEREST 1

RELATED APPEALS AND INTERFERENCES 1

STATUS OF CLAIMS 1

STATUS OF AMENDMENTS 1

SUMMARY OF CLAIMED SUBJECT MATTER 2

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL:

I. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") Been Established? 7

II. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and the Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter"), further in view of Basic & Clinical Pharma., 6th Ed. (1995) 529 ("Katzung") Been Established? 7

ARGUMENT 7

I. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") has Failed to be Established 7

A. The Rejection 7

B. The Prior Art 8

C. Discussion 8

II. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter"), further in view of Basic & Clinical Pharma., 6th Ed. (1995) 529 ("Katzung")

has Failed to be Established..... 13

A. The Rejection..... 13
B. The Prior Art..... 13
C. Discussion..... 14

CLAIMS APPENDIX..... 16
EVIDENCE APPENDIX..... 33
RELATED PROCEEDINGS APPENDIX..... 33

I

REAL PARTY IN INTEREST

The real party in interest in this Appeal is assignee Schering Corporation, having a principal place of business 2000 Galloping Hill Road, Kenilworth, NJ 07033.

II

RELATED APPEALS AND INTERFERENCES

As the legal representative of Appellant, the undersigned attorney has no knowledge of any appeals or interferences directly related to this Appeal.

III

STATUS OF CLAIMS

This is an original patent application in which claims 1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47, 48, 83, 84, 86, 100 and 101 are pending in this application. Claims 5-10, 14-20, 22-31, 33, 35, 36, 41, 44-46, 49-82, 85 and 87-99 have been withdrawn by the Examiner as being drawn to a non-elected invention.

Claims 1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47-48, 83, 86 and 100-101 (pending) were finally rejected under 35 U.S.C. §103(a) in an Office Action mailed September 20, 2004 ("Final Office Action").

Twenty-three (23) pending claims (1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47-48, 83, 86 and 100-101) are at issue in this Appeal.

IV

STATUS OF AMENDMENTS

No claims were amended after final rejection. A copy of the claims involved in this Appeal is contained in the Appendix attached hereto.

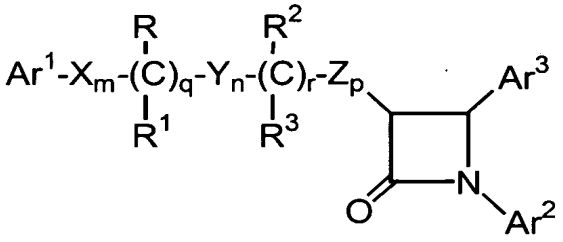
V

SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment set forth in claim 1, Applicants have discovered a composition comprising:

(a) at least one peroxisome proliferator-activated receptor (PPAR) activator; and

(b) at least one sterol absorption inhibitor represented by Formula (I):



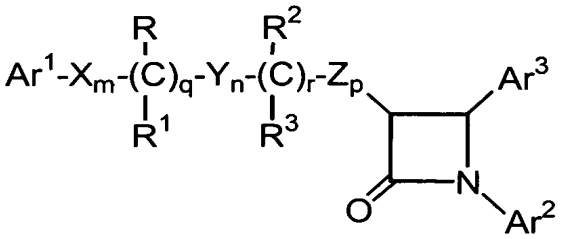
(I)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 1 for moiety definitions). See original claim 1 and page 3, line 6 - page 4, line 17 of the specification.

In another embodiment set forth in Claim 37, Applicants have discovered a therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (I):



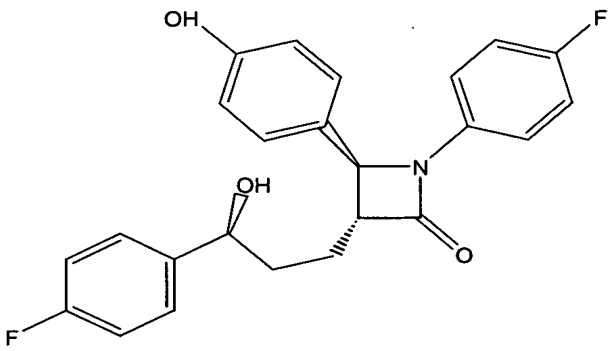
(I)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 37 for moiety definitions). See original claim 37 and page 21, line 27 - page 22, line 7 of the specification.

In another embodiment set forth in Claim 42, Applicants have discovered a composition comprising:

(a) at least one fibric acid derivative; and

(b) a compound represented by Formula (II) below:



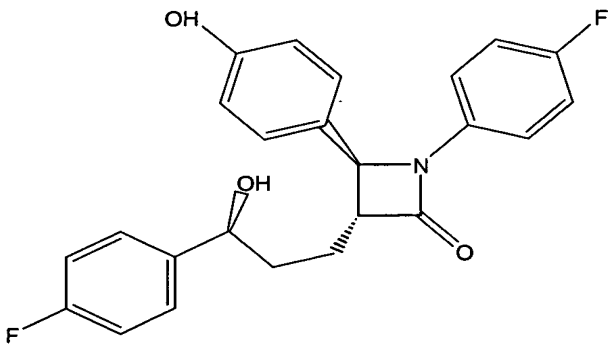
(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof. See original claim 42 and page 4, lines 18-22 of the specification.

In another embodiment set forth in Claim 48, Applicants have discovered a therapeutic combination comprising:

(a) a first amount of at least one fibric acid derivative; and

(b) a second amount of a compound represented by Formula (II) below:



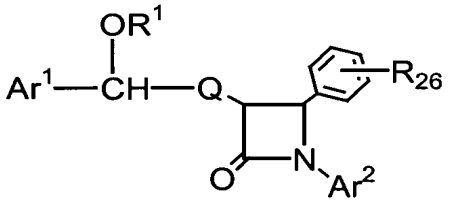
(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 48 and page 4, lines 18-22 of the specification.

In another embodiment set forth in Claim 83, Applicants have discovered a composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (IX):



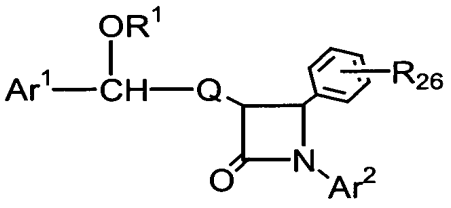
(IX)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 83 for moiety definitions). See original claim 83 and page 18, line 24 - page 21, line 26 of the specification.

In another embodiment set forth in Claim 86, Applicants have discovered a therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (IX):



(IX)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. (see original claim 86 for moiety definitions). See original claim 86 and page 4, lines 18-22 of the specification.

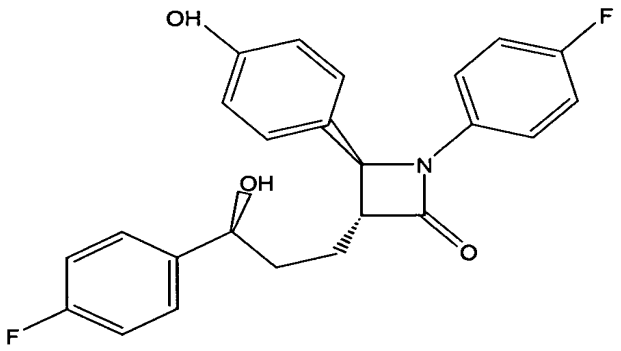
In another embodiment set forth in Claim 100, Applicants have discovered a composition comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, pharmaceutically acceptable salts or solvates, or prodrugs thereof. See original claim 100 at page 162, lines 1-7 of the specification.

In another embodiment set forth in Claim 101, Applicants have discovered a therapeutic combination comprising (a) a first amount of at least one antioxidant or vitamin and (b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound compound or isomers thereof, pharmaceutically acceptable salts or solvates, or prodrugs thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 101 at page 162, lines 7-18 of the specification.

In the Office Action of July 2, 2003, Applicants were required to elect a species of peroxisome proliferator-activated receptor (PPAR) activator, sterol absorption inhibitor, and third therapeutic agent.

Applicants provisionally elected with traverse fenofibrate as the PPAR activator. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Response") at page 2, lines 8-9.

Applicants provisionally elected with traverse ezetimibe as the sterol absorption inhibitor, represented by Formula (II) below:



(II).

Ezetimibe is the active ingredient in ZETIA™ (ezetimibe) pharmaceutical formulation and VYTORIN™ (ezetimibe/simvastatin) pharmaceutical formulation, both of which are commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Response") at page 2, lines 12-13.

In the same Response, Applicants provisionally elected niacin as the third therapeutic agent. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Response") at page 2, lines 15-16.

The claimed compositions and combinations can be useful for treating vascular conditions, diabetes, obesity and/or lowering concentration of a sterol in plasma in a mammal (page 22, lines 8-15 of the specification).

VI

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") Been Established?

II. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and the Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter"), further in view of Basic & Clinical Pharma., 6th Ed. (1995) 529 ("Katzung") Been Established?

VII

ARGUMENT

I. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") has Failed to be Established

A. The Rejection

Claims 1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47-48, 83, 86 and 100-101 have been rejected under 35 U.S.C. §103(a) as obvious over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter").

The reasons for rejection are set forth in the Final Office Action, summarized as follows:

Rosenblum et al. disclose that the elected compound of Formula II, ezetimibe, is useful for reducing cholesterol and the risk of atherosclerosis (Final Office Action at page 4). Medical Letter teaches fenofibrate as useful in reducing serum cholesterol (Final Office Action at page 4).

It is acknowledged that the primary references do not expressly teach the claimed composition comprising ezetimibe and fenofibrate (Final Office Action at page 4).

It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine ezetimibe and fenofibrate, since the cited prior art teaches that both ezetimibe and fenofibrate are useful in reducing serum cholesterol individually, citing *In re Kerkoven*, 205 U.S.P.Q. 1069 (Final Office Action at pages 4-5).

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (Page 29, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims).

Medical Letter teaches fenofibrate as useful in reducing VLDL cholesterol and triglycerides (Medical Letter at page 68).

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1-4, 11-13, 34, 37-40, 42, 43, 47, 48, 83, 84 and 86

Claims 1 and 37 recite a composition and therapeutic combination, respectively, comprising a sterol absorption inhibitor of Formula I shown above, isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; and at least one PPAR activator.

Claims 2 and 38 depend from claims 1 and 37, respectively, and recite that the at least one PPAR activator is a fibric acid derivative.

Claim 3 depends from claim 2 and recites that the fibric acid derivative is selected from, *inter alia*, fenofibrate. Claim 4 depends from claim 3 and recites that the fibric acid derivative is fenofibrate.

Claim 13 depends from claim 1 and recites that the amount of sterol absorption inhibitor administered to a mammal ranges from about 0.1 to about 1000 mg/day.

Claim 34 recites a pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 1 and carrier.

Claim 39 depends from claim 37 and recites that the PPAR activator is administered concomitantly with the sterol absorption inhibitor.

Claim 40 depends from claim 37 and recites that the PPAR activator and the sterol absorption inhibitor are present in separate treatment compositions.

Claims 42 and 48 recite a composition and therapeutic combination, respectively, comprising ezetimibe and at least one fibric acid derivative.

Claim 43 depends from claim 42 and recites that the fibric acid derivative is fenofibrate.

Claim 47 recites a pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 42 and carrier.

Claims 83 and 86 recite a composition and therapeutic combination, respectively, comprising a sterol absorption inhibitor of Formula IX shown above, isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; and at least one PPAR activator.

Claim 84 pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 83 and carrier.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of sterol absorption inhibitor (such as that of Formula (I) (e.g., ezetimibe)) and PPAR activator (such as fenofibrate).

Neither Rosenblum et al. nor Medical Letter provides motivation for substituting a PPAR activator for the statin used in combination with ezetimibe described in Rosenblum et al. As disclosed in the Medical Letter Clinical Study section at page 68, fenofibrate is not as effective as statins in lowering LDL cholesterol, a major risk factor in atherogenesis. Since statins are more effective in lowering LDL cholesterol, there is no motivation to substitute a PPAR activator such as fenofibrate for the statin in the combination disclosed in Rosenblum et al.

There is no guidance provided by Rosenblum et al. nor Medical Letter to pick and choose among numerous cholesterol treatments to select the particularly claimed combination of sterol absorption inhibitor (such as that of Formula (II) (e.g., ezetimibe)) and PPAR activator (such as fenofibrate).

Therefore, the prima facie case of obviousness based upon Rosenblum et al. and Medical Letter has not been established and the rejection of claims 1-4, 11-13, 34, 37-40, 42, 43, 47, 48, 83, 84 and 86 should be reconsidered and withdrawn.

Claims 21, 28 and 32

Claims 21 and 28 depend from claim 1 and recite that the composition further comprises nicotinic acid, niceritrol, nicofuranose or acipimox. Thus the composition would comprise sterol absorption inhibitor, PPAR activator such as fenofibrate, and niacin.

Claim 32 depends from claim 1 and recites that the composition further comprises at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

With respect to claims 21 and 32, Rosenblum et al. nor Medical Letter, taken alone or together as suggested in the Office Action, provides any motivation for a triple combination treatment of sterol absorption inhibitor (such as that of Formula (II) (e.g., ezetimibe)), PPAR activator (such as fenofibrate) and niacin. These references provide no guidance or motivation as to the desirability for such as combination or selecting the particular components of the combination, or the potential effect of drug-drug interactions. For example, in the Drug Interaction section at page 69, Medical Letter discloses that it is unclear whether, *like gemfibrozil and niacin*, concurrent administration of fenofibrate with a statin could increase the risk of rhabdomyolysis. In the Advisory Action of December 7, 2004, the Examiner

encourages Applicants to bring forth evidence of potential drug-drug interaction. This evidence is present in the Drug Interaction section at page 69 of Medical Letter cited in the rejection as pointed out above and the burden therefore is shifted to the Examiner to refute the teaching in the reference which was cited in the rejection.

Because of the difference of the way that each component of the presently claimed combination acts, it is respectfully submitted that the rejection is based upon an improper combination of references.

Therefore, the prima facie case of obviousness based upon Rosenblum et al. and Medical Letter has not been established and the rejection of claims 21, 28 and 32 should be reconsidered and withdrawn.

Claims 100 and 101

Claims 100 and 101 recite a composition or therapeutic combination comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers, prodrugs, salts or solvates thereof.

Applicants wish to emphasize that claim 1 does not require the presence of a PPAR activator.

With respect to patentability of the composition or combination of Claims 100 and 101, neither Rosenblum nor Medical Letter suggests or disclose combinations of a sterol absorption inhibitor and antioxidant or vitamin.

Therefore, the prima facie case of obviousness based upon Rosenblum et al. and Medical Letter has not been established and the rejection of claims 100 and 101 should be reconsidered and withdrawn.

Accordingly, Applicants respectfully request that the § 103(a) rejection of claims 1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47-48, 83, 86 and 100-101 be reconsidered and withdrawn.

II. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter"), further in view of Basic & Clinical Pharma., 6th Ed. (1995) 529 ("Katzung") has Failed to be Established

A. The Rejection

Claims 21 and 32 were rejected under 35 U.S.C. §103(a) as obvious over Rosenblum et al. and the Medical Letter, further in view of Basic & Clinical Pharma., 6th Ed. (1995) 529 ("Katzung").

The reasons for rejection are set forth in the Final Office Action, summarized as follows:

Rosenblum et al. and Medical Letter suggest a composition containing fenofibrate and ezetimibe (Final Office Action at page 5).

It is acknowledged that the primary references do not expressly teach the claimed composition containing niacin (Final Office Action at page 5).

Katzung teaches niacin as useful for lowering cholesterol (Final Office Action at page 5).

It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate niacin into the ezetimibe and fenofibrate composition, since the cited prior art teaches that all three ingredients are useful in reducing serum cholesterol, citing *In re Kerkoven*, 205 U.S.P.Q. 1069 (Final Office Action at page 5).

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (Page 29, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims). Rosenblum et al. do not disclose niacin.

Medical Letter teaches fenofibrate as useful in reducing VLDL cholesterol and triglycerides (Medical Letter at page 68). Medical Letter discloses that niacin is a drug for treating hypertriglyceridemia (Medical Letter at page 69). Medical Letter does not suggest or disclose a combination of substituted azetidinone compound, PPAR activator and niacin.

Katzung discloses that niacin decreases VLDL and LDL levels in patients (Katzung at 529). Katzung does not suggest or disclose a combination of substituted azetidinone compound, PPAR activator and niacin.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

Claim 21 depends from claim 1 and recites that the composition further comprises nicotinic acid, niceritrol, nicofuranose or acipimox. Thus the composition would comprise sterol absorption inhibitor, PPAR activator such as fenofibrate, and niacin.

Claim 32 depends from claim 1 and recites that the composition further comprises at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

With respect to claims 21 and 32, Rosenblum et al. nor Medical Letter, taken alone or together as suggested in the Office Action, provides any motivation for a triple combination treatment of sterol absorption inhibitor (such as that of Formula (II) (e.g., ezetimibe)), PPAR activator (such as fenofibrate) and niacin. These references provide no guidance or motivation as to the desirability for such as combination or selecting the particular components of the combination, or the potential effect of drug-drug interactions. For example, in the Drug Interaction section at page 69, Medical Letter discloses that it is unclear whether, *like gemfibrozil and niacin*, concurrent administration of fenofibrate with a statin could increase the risk of

rhabdomyolysis. In the Advisory Action of December 7, 2004, the Examiner encouraged Applicants to bring forth evidence of potential drug-drug interaction. This evidence is present in the Drug Interaction section at page 69 of Medical Letter cited in the rejection as pointed out above and the burden therefore is shifted to the Examiner to refute the teaching in the reference which was cited in the rejection.

Katzung provides no further incentive to one skilled in the art to include niacin in a composition or therapeutic combination of sterol absorption inhibitor and PPAR activator.

Because of the difference of the way that each component of the presently claimed combination acts, it is respectfully submitted that the rejection is based upon an improper combination of references.

Therefore, the prima facie case of obviousness based upon Rosenblum et al., Medical Letter and Katzung has not been established and the rejection of claims 21 and 32 should be reconsidered and withdrawn.

Respectfully submitted,

Date: January 12, 2005

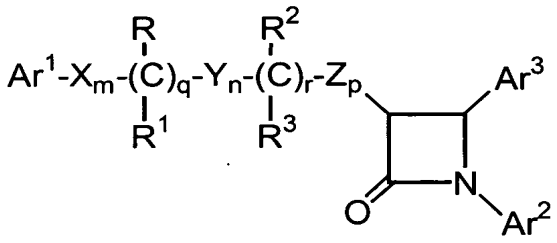
Ann Marie Cannoni
Registration No. 35,972
Webb Ziesenheim Logsdon Orkin & Hanson, P.C.
700 Koppers Building
Pittsburgh, PA 15219
Phone: (412) 471-8815
Fax: (412) 471-4094
E-mail: acannoni@webblaw.com

CLAIM APPENDIX

1. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of
$-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$,
$-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

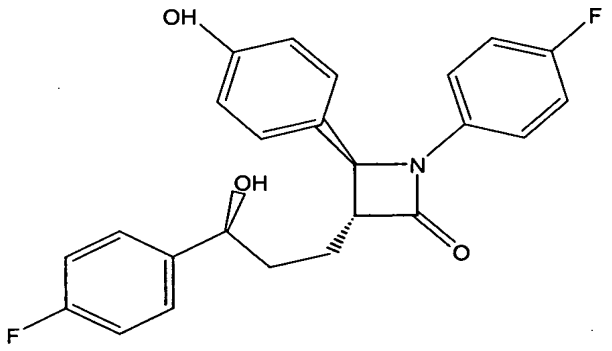
2. The composition according to claim 1, wherein the at least one peroxisome proliferator-activated receptor activator is a fibric acid derivative.

3. The composition according to claim 2, wherein the fibric acid derivative is selected from the group consisting of fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate, lifibrol and mixtures thereof.

4. The composition according to claim 3, wherein the fibric acid derivative comprises fenofibrate.

11. The composition according to claim 1, wherein the at least one peroxisome proliferator-activated receptor activator is administered to a mammal in an amount ranging from about 50 to about 3000 milligrams of peroxisome proliferator-activated receptor activator per day.

12. The composition according to claim 1, wherein the sterol absorption inhibitor is represented by Formula (II) below:



(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

13. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is administered to a mammal in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

21. The composition according to claim 1, further comprising nicotinic acid, niceritrol, nicofuranose or acipimox.

28. The composition according to claim 1, further comprising at least one antioxidant or vitamin.

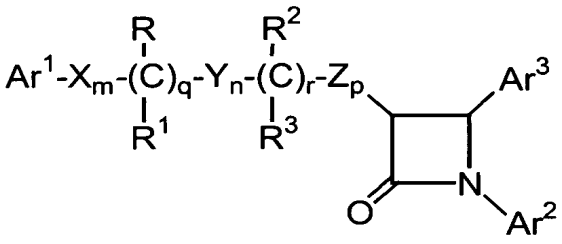
32. The composition according to claim 1, further comprising at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

34. A pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

37. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of -OR^6,

-O(CO)R^6, -O(CO)OR^9 and -O(CO)NR^6R^7;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5

or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

38. A therapeutic combination according to claim 37, wherein the at least one peroxisome proliferator-activated receptor activator is a fibric acid derivative.

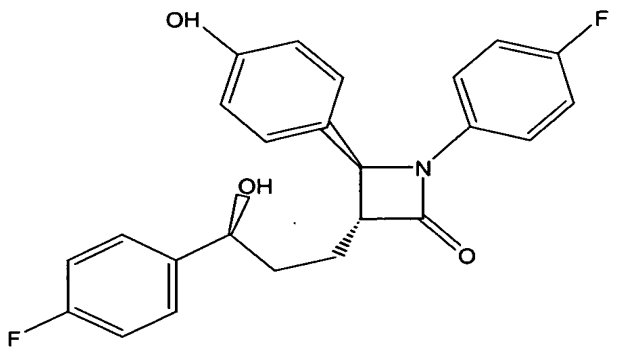
39. A therapeutic combination according to claim 37, wherein the at least one peroxisome proliferator-activated receptor activator is administered concomitantly with the at least one sterol absorption inhibitor.

40. A therapeutic combination according to claim 37, wherein the at least one peroxisome proliferator-activated receptor activator and the at least one sterol absorption inhibitor are present in separate treatment compositions.

42. A composition comprising:

(a) at least one fibric acid derivative; and

(b) a compound represented by Formula (II) below:



(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

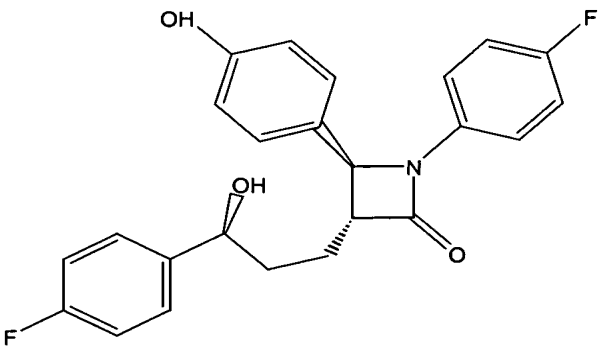
43. The composition according to claim 42, wherein the fibric acid derivative is fenofibrate.

47. A pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 42 and a pharmaceutically acceptable carrier.

48. A therapeutic combination comprising:

(a) a first amount of at least one fibric acid derivative; and

(b) a second amount of a compound represented by Formula (II) below:

(a) 

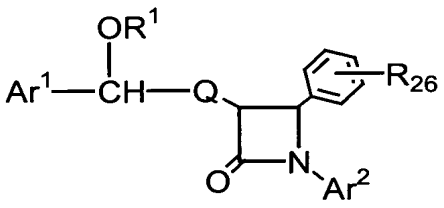
(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof,
wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

83. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (IX):



(IX)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,

R^{26} is selected from the group consisting of:

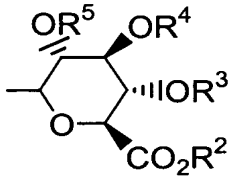
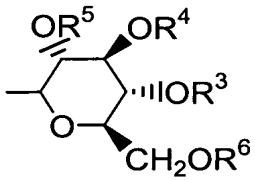
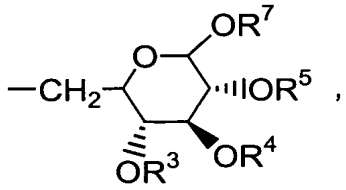
a) OH;

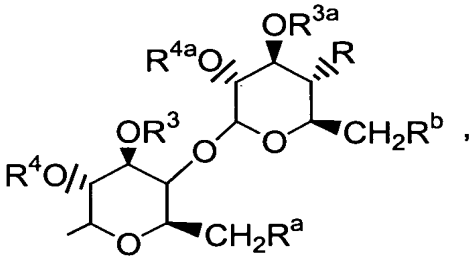
b) OCH_3;

c) fluorine and

d) chlorine;

R^1 is selected from the group consisting of

H,  ,  ,  ,

 , -SO_3H; natural and unnatural amino acids;

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy and -W-R^{30};

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-C_6)alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, -C(O)$(C_1$-$C_6)$alkyl and -C(O)aryl;

R^{30} is independently selected form the group consisting of R^{32}-substituted T, R^{32}-substituted-T-$(C_1$-$C_6)$alkyl, R^{32}-substituted-$(C_2$-$C_4)$alkenyl, R^{32}-substituted-$(C_1$-$C_6)$alkyl, R^{32}-substituted-$(C_3$-C7)cycloalkyl and R^{32}-substituted-$(C_3$-C7)cycloalkyl$(C_1$-$C_6)$alkyl;

R^{31} is independently selected from the group consisting of H and $(C_1$-$C_4)$alkyl;

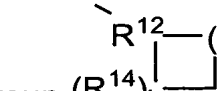
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of H, halogeno, $(C_1$-$C_4)$alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, $(C_1$-$C_4)$alkoxy, methylenedioxy, oxo, $(C_1$-$C_4)$alkylsulfanyl, $(C_1$-$C_4)$alkylsulfinyl, $(C_1$-$C_4)$alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH$(C_1$-$C_4)$alkyl, -C(O)-N$((C_1$-$C_4)$alkyl$)_2$, -C(O)-$(C_1$-$C_4)$alkyl, -C(O)-$(C_1$-$C_4)$alkoxy and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a $(C_1$-$C_4)$alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar^1 is aryl, R^{10}-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

Ar^2 is aryl or R^{11}-substituted aryl;

Q is $-(CH_2)_q-$, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,

forms the spiro group  ;

R^{12} is

$-\overset{|}{C}H-$, $-\overset{|}{C}(C_1\text{-}C_6\text{ alkyl})-$, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_4\text{-}R^{23})-$, $-\overset{|}{N}-$, or $-\overset{|}{\overset{|}{\overset{+}{N}}}O^-$;

R^{13} and R^{14} are independently selected from the group consisting of $-CH_2-$,

$-CH(C_1\text{-}C_6\text{ alkyl})-$, $-C(\text{di-}(C_1\text{-}C_6)\text{ alkyl})$, -CH=CH- and $-C(C_1\text{-}C_6\text{ alkyl})=CH-$;

or R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a

-CH=CH- or a $-CH=C(C_1\text{-}C_6\text{ alkyl})-$ group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is -CH=CH- or $-C(C_1\text{-}C_6\text{ alkyl})=CH-$, a is 1; provided that when R^{14} is -CH=CH- or $-C(C_1\text{-}C_6\text{ alkyl})=CH-$, b is 1; provided that when a is 2 or 3, the R^{13}'s can be the same or different; and provided that when b is 2 or 3, the R^{14}'s can be the same or different;

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl,

$-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1\text{-}5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$,

$-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$,

$-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $-S(O)_{0\text{-}2}R^{21}$, $-O(CH_2)_{1\text{-}10}-COOR^{19}$,

$-O(CH_2)_{1-10}CONR^{19}R^{20}$, $-(C_1-C_6$ alkylene$)-COOR^{19}$, $-CH=CH-COOR^{19}$, $-CF_3$,

-CN, $-NO_2$ and halogen;

R^{19} and R^{20} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl-substituted (C_1-C_6)alkyl;

R^{21} is (C_1-C_6)alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, (C_1-C_6)alkyl, aryl (C_1-C_6)alkyl, $-C(O)R^{19}$ or $-COOR^{19}$;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -COOH, NO_2, $-NR^{19}R^{20}$, -OH and halogeno; and

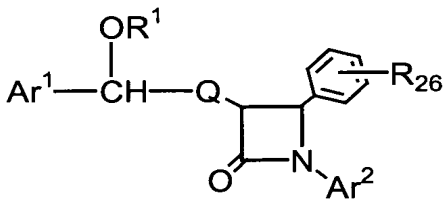
R^{25} is H, -OH or (C_1-C_6)alkoxy.

84. A pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 83 and a pharmaceutically acceptable carrier.

86. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (IX):



(IX)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,

R^{26} is selected from the group consisting of:

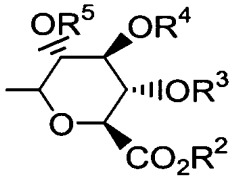
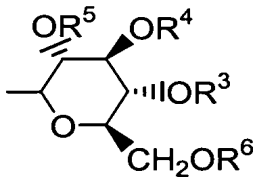
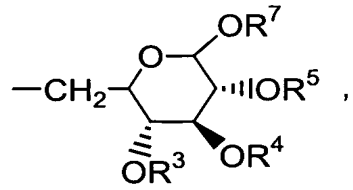
a) OH;

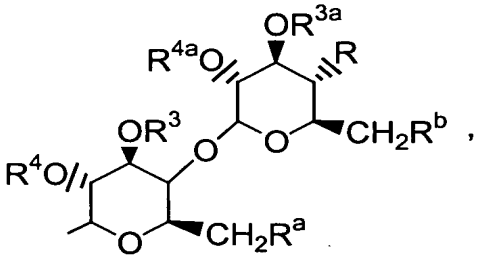
b) OCH_3;

c) fluorine and

d) chlorine;

R^1 is selected from the group consisting of

H,  ,  ,  ,

 , -SO_3H; natural and unnatural amino acids;

R; R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$-alkoxy and -W-R^{30};

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, aryl and aryl$(C_1\text{-}C_6)$alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, -C(O)$(C_1$-$C_6)$alkyl and -C(O)aryl;

R^{30} is independently selected form the group consisting of R^{32}-substituted T, R^{32}-substituted-T-$(C_1$-$C_6)$alkyl, R^{32}-substituted-$(C_2$-$C_4)$alkenyl, R^{32}-substituted-$(C_1$-$C_6)$alkyl, R^{32}-substituted-$(C_3$-C7)cycloalkyl and R^{32}-substituted-$(C_3$-C7)cycloalkyl$(C_1$-$C_6)$alkyl;

R^{31} is independently selected from the group consisting of H and $(C_1$-$C_4)$alkyl;

T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of H, halogeno, $(C_1$-$C_4)$alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, $(C_1$-$C_4)$alkoxy, methylenedioxy, oxo, $(C_1$-$C_4)$alkylsulfanyl, $(C_1$-$C_4)$alkylsulfinyl, $(C_1$-$C_4)$alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH$(C_1$-$C_4)$alkyl, -C(O)-N$((C_1$-$C_4)$alkyl$)_2$, -C(O)-$(C_1$-$C_4)$alkyl, -C(O)-$(C_1$-$C_4)$alkoxy and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a $(C_1$-$C_4)$alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar^1 is aryl, R^{10}-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

Ar^2 is aryl or R^{11}-substituted aryl;

Q is $-(CH_2)_q-$, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,

forms the spiro group ;

R^{12} is

-CH-, -C(C_1-C_6 alkyl)-, -CF-, -C(OH)-, -C(C_6H_4-R^{23})-, -N-, or $-{}^{+}NO^{-}$;

R^{13} and R^{14} are independently selected from the group consisting of -CH_2-,
-CH(C_1-C_6 alkyl)-, -C(di-(C_1-C_6) alkyl), -CH=CH- and -C(C_1-C_6 alkyl)=CH-; or R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a
-CH=CH- or a -CH=C(C_1-C_6 alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is -CH=CH- or -C(C_1-C_6 alkyl)=CH-, a is 1; provided that when R^{14} is
-CH=CH- or -C(C_1-C_6 alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R^{13}'s can be the same or different; and provided that when b is 2 or 3, the R^{14}'s can be the same or different;

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C_1-C_6)alkyl,
-OR^{19}, -O(CO)R^{19}, -O(CO)OR^{21}, -O(CH_2)$_{1-5}OR^{19}$, -O(CO)$NR^{19}R^{20}$, -$NR^{19}R^{20}$,
-NR^{19}(CO)R^{20}, -NR^{19}(CO)OR^{21}, -NR^{19}(CO)$NR^{20}R^{25}$, -$NR^{19}SO_2R^{21}$, -$COOR^{19}$,
-$CONR^{19}R^{20}$, -COR^{19}, -$SO_2NR^{19}R^{20}$, -S(O)$_{0-2}R^{21}$, -O(CH_2)$_{1-10}$-$COOR^{19}$,

$-O(CH_2)_{1-10}CONR^{19}R^{20}$, $-(C_1-C_6$ alkylene$)-COOR^{19}$, $-CH=CH-COOR^{19}$, $-CF_3$,

$-CN$, $-NO_2$ and halogen;

R^{19} and R^{20} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl-substituted (C_1-C_6)alkyl;

R^{21} is (C_1-C_6)alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, (C_1-C_6)alkyl, aryl (C_1-C_6)alkyl, $-C(O)R^{19}$ or $-COOR^{19}$;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -COOH, NO_2, $-NR^{19}R^{20}$, -OH and halogeno; and

R^{25} is H, -OH or (C_1-C_6)alkoxy,

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

100. A composition comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.

101. A therapeutic combination comprising (a) a first amount of at least one antioxidant or vitamin and (b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or

isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.